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Original research article

Tumour volumes: Predictors of early treatment response in locally advanced head and neck cancers treated with definitive chemoradiation

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ARTICLE INFO

Article history:
Received 14 March 2016
Accepted 8 April 2016
Available online 5 May 2016

Keywords:
Chemoradiation
Early response
Head neck
Prognostic factors
Tumour volume

ABSTRACT

Aim: To analyse and predict early response 3 months post definitive chemoradiation (CCRT) utilising tumour volume (TV) measurement in locally advanced head and neck cancers (LAHNC).

Background: LAHNC are 3-dimentional lesions. The largest diameter of these tumours measured for T-classification may not necessarily reflect the true tumour dimensions. TV accurately reflects the tumour burden because it is a measurement of tumour burden in all three dimensions.

Materials and methods: It is a single institutional prospective study including 101 patients with LAHNC treated with definitive CCRT. TV data noted were primary tumour volume (PTV), total nodal volume (TNV) and total tumour volume (TTV). Response evaluation was done at 3 months after the completion of definitive CCRT and patients were categorised either having achieved complete response (CR) or residual disease.

Results: Patients who had not achieved CR were found to have larger TV compared with those who had achieved CR. There were significant inverse correlations between PTV and response (median 16.37 cm^3 vs. 45.2 cm^3; $p = 0.001$), and between TTV and response (median 36.14 cm^3 vs. 66.06 cm^3; $p < 0.001$). Receiver operating characteristic (ROC) analysis identified an "optimal cut-off" value of 41 cm^3 for PTV and 42 cm^3 for TTV above and below which the magnitude of difference in response was the greatest.

Conclusions: If response evaluation 3 months post CCRT is to be predicted it is simply not enough to measure the largest single dimension of the tumour. TV seems to be a better and more accurate reflection of the true total tumour burden or extent of the disease.

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http://dx.doi.org/10.1016/j.rpor.2016.04.002

1. Background

Head and neck cancers (HNC), particularly locally advanced, are a group of heterogeneous tumours and are diverse in their natural history and behaviour. To understand and bring this diversity into clinical use, the American Joint Committee on Cancer (AJCC) uses a TNM staging system. Amongst many others, the purpose of this staging system is to predict prognosis.

The TNM system is an expression of the anatomic extent of disease. T classification in TNM staging system depends mainly on the measurement of maximum single dimension of the primary tumour. Although this system of staging is user-friendly, universally applicable and provides the basis for most cancer care and research, it is felt that this system has certain limitations. Firstly, HNC are 3-dimensional lesions, not only spreading into different planes and directions within the head and neck region but also with unequal rate of spread/invasion/infiltration into the surrounding tissues. Hence, the largest diameter of tumour measured for T classification may not necessarily reflect the true tumour dimensions. Indeed, studies have shown that there is a significant variation in the tumour volumes within the same T-classification.[1,2] This reflects the poor ability of T-classification to describe true dimensions of locally advanced head and neck cancers (LAHNC). Secondly, for certain sites, T-classification takes into account tumour features which are mainly important for surgeons to decide on operability or resectability, such as invasion and infiltration of primary tumour into surrounding important structures. Although this information is of paramount significance to surgeons, it is not so for a non-surgical treatment modality such as definitive radiotherapy (RT) or concurrent chemoradiation (CCRT).

Thus, there is a need to take into account certain other feature(s) of these heterogeneous tumours, besides maximum single dimension, which can reflect the total tumour burden more accurately. While doing so we must also ensure that we do not lose out the very vital information about the anatomical extent of disease provided by the TNM staging system.

Tumour develops from a single transformed cell. In order to completely sterilise a tumour by RT or, in other words, achieve complete response at the end of RT, every single clonogenic cell capable of tumour growth has to be killed. Many authors have shown that the number of clonogenic cells increases almost linearly with increase in tumour load and thus tumour volume (TV).[3,4] But it was Fletcher who first proved that there does exist a direct relationship between clonogen numbers and TV.[5] Hence, it seems that there exists a relationship between the probability of tumour response to RT and the TV. There is growing evidence recognising positive correlation between TV and prognosis.[6–8] Knegjens et al.[9] have shown TV to be a good predictor of early response to RT, there being larger TV in those with residual disease.

2. Aim

This study aims at analysing and predicting early response (3 months post definitive CCRT) utilising TV data in patients with LAHNC in the era of intensity modulated RT (IMRT). While doing so we will also discuss various ways in which TV data can be incorporated in day to day clinical practice to predict early response and few related issues.

3. Materials and methods

It was a single institutional prospective study conducted from June 2013 to April 2015. In the study, 108 newly diagnosed patients with LAHNC treated with definitive CCRT were recruited. All patients provided informed consent for the proposed treatment. Clearance from the institute's review and scientific committee board was obtained. Patient inclusion criteria were histologically proven squamous cell carcinoma of any grade, oropharyngeal, hypopharyngeal or laryngeal primary sites, accurately TNM staged locally advanced disease – stage III or IV non-metastatic disease, clear and well visualised primary and nodal disease on diagnostic imaging, age >18 years, no co-existing or prior malignancy in the head and neck region, no prior RT to the head and neck region, and eastern cooperative oncology group status ≤2. All underwent staging as per AJCC recommendations. The pre-treatment work up included detailed history, physical examination, and endoscopic assessment for primary tumour extent and to rule out synchronous malignancy. ^{18}F-fluorodeoxy-D-glucose (^{18}F-FDG) positron emission tomography–computed tomography (PET CT) was done to assess for loco-regional tumour extent and distant metastasis. All patients were planned for definitive CCRT.

3.1. *Diagnostic imaging, RT planning and simulation, and tumour volume measurement*

PET-CT scans were performed using full ring dedicated PET scanner (Siemens Biograph scanner, Lutetium Oxyorthosilicate crystal based 40 slice scanner) in 3D mode. Non-contrast CT scans (120 kV, 80 mA) were performed for attenuation correction and anatomical localisation. Standard whole body PET-CT scans were acquired from skull base to mid-thigh. The acquisition time was 120–180 s/bed position. An appropriate head rest was used during PET-CT. After the diagnostic scan was done, the table couch was changed to a flat table couch. The patients were immobilised with ordinary head, neck and shoulder thermoplastic orfit cast along with the same head rest as used during PET-CT. Alignment was ensured with the help of lasers. Planning CT scans were done with slice thickness of 3 mm from the vertex of skull to carina. The regional scan was taken with the same set up criteria as that of planning CT scan. All data sets were sent by way of Digital Imaging and Communications in Medicine to SomaVision v10 (Varian Medical System, Palo Alto, CA) radiation planning workstation. The contrast-enhanced CT simulation scans were fused with PET-CT scans using ECLIPSE v10 (Varian Medical System, Palo Alto, CA) using automatic image registration algorithm. Fine manual adjustments were required in most cases for more precise fusion. Target volumes and organs at risk (OARs) were contoured.

For the purpose of this research, various TV delineated were as follows: primary tumour volume (PTV) – volume occupied by macroscopic visible primary tumour, yielding the gross